HFA-305

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

John Tomaszewski
Director, Regulatory Affairs
Sterling Health
Division of Sterling Winthrop, Inc.
90 Park Avenue
New York, New York 10016

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Re: Docket No. 78N-036L
Comment No. CP17

Dear Mr. Tomaszewski:

We refer to your above referenced citizen petition dated September 23, 1994.

The petition requests that magnesium hydroxide at a dosage of 1,200 mg taken in a single daily dose, be included in the final monograph for over-the-counter (OTC) laxative drug products (21 CFR 334) as a generally recognized safe and effective stool softener laxative indicated for the relief of occasional constipation.

For the following reason, the agency considers action on the petition completed:

> On August 3, 1995, Dr. Gilbertson issued a letter to you (copy enclosed) indicating that the data submitted in your petition are not sufficient to include magnesium hydroxide at a 1,200-mg daily dose as a stool softener laxative in the final monograph for OTC laxative drug products. Accordingly, your petition is denied.

If you have any questions regarding the petition, please refer to the docket and comment number above and submit all inquiries, in triplicate, to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Drive, Room 1-23, Rockville, MD 20857.

Sincerely yours,

Ronald G. Chesemore
Associate Commissioner
for Regulatory Affairs

Enclosure

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Laxative
Feedback

August 3, 1995

John Tomaszewski
Director, Regulatory Affairs
Sterling Health
Division.of Sterling Winthrop, Inc.
90 Park Avenue
New York, New York 10016

Re: Docket No. 78N-036L
Comment No. CP17

Dear Mr. Tomaszewski:

This is in response to your company's citizen petition dated September 23, 1994, filed as Comment No. CP17 under Docket No. 78N-036L in FDA's Dockets Management Branch on October 6, 1994. The petition requested that magnesium hydroxide at a dosage of 1,200 mg, taken in a single daily dose, be included in the final monograph for OTC laxative drug products (21 CFR 334) as a generally recognized safe and effective stool softener laxative active ingredient indicated for the relief of occasional constipation . To support the request, two clinical studies (GSA 90-09 and GSA 91-01) were submitted. Both studies employed a double-blind, randomized, placebo-controlled, double dummy, crossover design.

The Office of OTC Drug Evaluation has reviewed your petition and finds the data inadequate to support the effectiveness of 1,200 mg of magnesium hydroxide as a Category I stool softener laxative.

In study GSA 90-09, the effectiveness of magnesium hydroxide as a stool softener laxative was compared with a marketed stool softener laxative, docusate sodium, in 18 normal subjects. Two subjects dropped out before completing the crossover and, therefore, were not included in the final statistical analysis. The 16 subjects completing the study were housed for 14 consecutive days during each of the three treatment periods with a 14-day washout period between each treatment period for a total study period of 10 weeks. Because magnesium hydroxide suspension and the docusate sodium capsules were different dosage forms, to ensure blinding, each subject in the three treatment groups received a single dose of 2 capsules and 15 ml of suspension. The treatment medications were magnesium hydroxide suspension (1,200 mg/15 ml) or placebo suspension, two docusate sodium capsules (100 mg each), or two placebo capsules at bedtime.

Six efficacy parameters were measured. The three objective parameters were total bowel movements (BM) per week, fecal weight, and fecal water content (the primary parameter). Total daily fecal samples were collected on days 8-14 and analyzed for weight and water content. The three subjective parameters were degree of consistency of bowel movements (watery, soft, hard), severity of cramps (none, mild, moderate, severe), and ease of bowel movements (comfortable, uncomfortable). Subjective parameters were recorded by subjects starting from day 1 and rated using a simple graded 2 to 4 point scale and a visual analog scale for additional comparisons for

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cramps and ease of bowel movements. Statistical analyses were by ANOVA.

The petition stated that the data for study GSA 90-09 showed that on days 12, 13, and 14, the fecal weights of subjects treated with magnesium hydroxide were significantly higher than the fecal weights of subjects treated with docusate sodium. Fecal water content was also significantly higher on days 8 to 14 for subjects treated with magnesium hydroxide than for subjects treated with docusate sodium. No statistically significant differences were detected in the number of bowel movements or the ease of bowel movements among the treatment groups .

The design of study GSA 91-01 was the same as that in study 90-09. Sixteen subjects were enrolled in the study and one subject dropped out due to continuing use of concomitant medication. The petition noted that the dropout occurred prior to completing the crossover and the incomplete data were not included in the final statistical analysis. The petition stated that the subjective rating scores for consistency of bowel movements were significantly higher for magnesium hydroxide (indicating softer stools) than docusate sodium and placebo. The scoring for the ease of bowel movements favored magnesium hydroxide and was statistically significant compared to placebo, but not significantly different from docusate sodium. The number of bowel movements for the magnesium hydroxide treatment group was significantly greater than the placebo treatment group, but not statistically significant compared to the docusate sodium group. Statistical comparisons for efficacy variables for both studies are presented in the following table:

	Study # GSA 90-09		**Study # GSA 91-01**	
	MgOH vs. Placebo	MgOH vs. Docusate Sodium	MgOH vs. Placebo	MgOH vs. Docusate Sodium
Fecal Water (%)	significant	significant	significant	significant
Fecal Weight	#	#	#	#
Number of BM	nonsignificant	nonsignificant	significant	nonsignificant
Consistency of BM	significant	significant	significant	significant
Severity of Cramps Simple Scale Visual Analog	nonsignificant nonsignificant	nonsignificant significant	nonsignificant nonsignificant	nonsignificant nonsignificant
Ease of BM Simple Scale Visual Analog	nonsignificant nonsignificant	nonsignificant nonsignificant	nonsignificant significant	nonsignificant nonsignificant

 # Statistically significant only during some of the treatment days.

The Office of OTC Drug Evaluation has reviewed these studies and finds that they do not support the safety and effectiveness of magnesium hydroxide as a stool softener laxative. We consider the primary effectiveness parameter, i.e., measurement of fecal water content during the second week, as an invalid endpoint for the OTC use of magnesium hydroxide as a stool softener. The primary parameter should have been measured during the first week of treatment in order to meet the agency's 7-day limitation of use for OTC laxative drug products.

The agency has concerns regarding the 8 to 14 day time period to produce the laxative effect. Although not replicated in study GSA 90-09, there appeared to be a statistically significant increase in bowel movements over 14 days, comparing magnesium hydroxide and placebo. In the tentative final monograph (TFM) for OTC laxative drug products (50 FR 2124 at 2129-2130), the agency considered constipation lasting longer than 1 week could signify a more serious condition such as diverticular disease of the colon, irritable bowel syndrome, or colon cancer and proposed to retain the 1-week use limitation warning. Further, the agency believes that the administration of OTC laxatives for longer than 1 week may increase the risk of safety concerns, such as elevated levels of magnesium, sodium, calcium, or potassium that may negatively impact such disease conditions as hypertension, heart disease, or kidney disease.

The agency also believes that consumers should be aware of how soon a laxative is expected to work. Therefore, the agency proposed time frames in which laxatives are expected to work (50 FR 2129). The agency considers it important to inform consumers that "stool softener" laxatives (oral dosage time frame 12 to 72 hours) do not result in as quick a laxative action as "saline" laxatives (oral dosage time frame 1/2 to 6 hours). Therefore, the time frames for the onset of laxative action for magnesium hydroxide (i.e., between 8 to 14 days) in both studies do not meet the agency's 1-week limitation for use or the time to onset of laxative action for either "stool softener" laxatives (12 to 72 hours) or "saline" laxatives (1/2 to 6 hours) and are not acceptable. However, we are aware that, in certain situations, longer than 1-week use may be necessary. In these cases, laxative therapy should be under the supervision of a physician.

In addition, we do not believe that magnesium hydroxide should be classified as a stool softener laxative. In the TFM (50 FR 2124 at 2129), the agency concurred with the Advisory Review Panel's definitions and classification of OTC laxatives based on their general mechanism of action (40 FR 12902 at 12906) with the exception of the term "hyperosmotic" for rectally administered glycerin and sorbitol. The agency's classification of laxatives is based on how a specific ingredient works in the bowels or on the stool (50 FR 2129). Therefore, magnesium hydroxide was classified as a saline laxative based on its action in the bowels of increasing the water content in the intestinal lumen by osmotic forces and peristalsis stimulation. Docusate sodium was classified as a stool softener laxative based on its direct action on the stool. The agency also described "stool softeners" in the TFM (50 FR 2144) as surface-active agents that lower surface tension when mixed with the stool, thereby allowing sufficient water and fat penetration to have a softening effect on the stool and easing bowel movement.

An increase of water in the stool is not specific to any one mechanism of action of laxative drugs.

Although some characteristic of stool content, such as increased water content, may be similar for both a saline and stool softener laxative (as well as for other laxatives such as bulk-forming laxatives), equivalent clinical results do not necessarily prove equivalent pharmacologic mechanisms of action. The clinical studies submitted did not demonstrate a mechanism of action.

We recognize that there may be some overlap between the pharmacological mechanisms of action of some OTC laxatives. For example, there has been some evidence suggesting that the laxative effect of docusate sodium may also be attributed to its ability to stimulate secretion of electrolytes and water in the colon and increasing the concentration of cyclic adenosine monophosphate in the colonic mucosal cells exposed to docusate sodium, although the exact mechanism of laxative action is not clear (40 FR 12902 at 12912). However, until there is more conclusive evidence of the specific pharmacological mechanism of action of docusate sodium, we consider the general classification and definition proposed in the TFM still applicable. We are not aware of any data to show that magnesium hydroxide works directly on the stool, rather than in the intestinal lumen, nor were such data provided in your petition. Therefore, based on the above definitions and criteria, we do not consider it appropriate to classify magnesium hydroxide as a stool softener laxative.

We have the following additional comments:

1. Both studies were in normal subjects rather than constipated subjects. Subjects who suffered from occasional constipation should have been included in the studies. The sample size was small and the demographics of the subjects were not provided. No baseline stool measurements based on the efficacy variables were established prior to study enrollment nor defined baselines taken prior to each crossover. These deficiencies make it difficult to extrapolate results to the target population.

2. Although a 2-week washout period should have been adequate in subjects with normal bowel habits, appropriate statistical analyses and discussion of results should have been done on each treatment period to rule out any possible carryover effects.

3. Dietary influences and fluid consumption were not adequately addressed in the reports. The menus mentioned in the study report were not included. It was noted that in study GSA 90-09, the meals for period 2 and 3 were larger than period 1 due to complaints of hunger among some subjects. Factors such as diet, diet changes, and fluid intake could affect the study outcomes.

4. The composition of the placebo suspension and gelcaps were not provided. For example, we do not know if these products contained lactose.

5. In study GSA 90-09, data on fecal weight and percent of stool water were missing in some subjects because of inadequate specimen collections. For example, on day 8, your company stated that only 30 of the 48 observations were available for analysis of stool water content. Thus, depending on the day of the study, the missing or improperly handled specimens accounted for a 10 to 38 percent loss of total available data for the study. This missing data could affect the final study results.

6. Although there were only three dropouts (i.e., 34 subjects enrolled, 31 subjects completed studies), an intent to treat analysis should have been provided.

7. Although the results of subjects' serum calcium and magnesium measurements taken at the end of each study period indicated that there were no significant differences among the three treatments in study GSA 90-09, subjects on magnesium hydroxide in study GSA 91-01 showed a significantly higher magnesium level than subjects on placebo. Your company stated that this increase, which averaged 6.4 percent (2.16 vs. 2.03 mg/dL) was not significant. However, the normal range reference standards from which the electrolyte values were compared should have been provided.

8. The randomization sequence used was incomplete. Because there are three possible treatments available (M=MgOH, C=Docusate Sodium, and P=Placebo) for the three 2-week treatment periods, there are six possible treatment sequences (MCP, MPC, CPM, CMP, PMC, and PCM). Your company chose only three of the six sequences (i.e., MCP, CPM, and PMC). A complete randomization sequence is necessary to eliminate possibilities of such biases as sequence, crossover, and/or carryover effects in order to provide a statistical basis for tests of significance (i.e., robust results) .

Based on the above, we conclude that the data submitted are not sufficient to include magnesium hydroxide at a 1,200 mg daily dose as a stool softener laxative in the final monograph for OTC laxative drug products. If your company wishes to study a lower dose of magnesium hydroxide as a saline laxative than the 2.4 to 4.8 g that was proposed in the TFM (50 FR 2155), which meets the appropriate 1-week limitation of use, adequate safety and effectiveness data need to be provided. Likewise, if you are interested in a lower dose of magnesium hydroxide as a saline laxative for professional use only for longer than 1 week, studies need to demonstrate the safe and effective use for longer than 1 week and that there is a specific need for such laxative therapy in a target population. We will be glad to review any study protocols that you wish to submit.

Any comments you may wish to make on the above information should be submitted in three copies, identified with the docket and comment numbers shown at the beginning of this letter, to the Dockets Management Branch (HFA-305), Food and Drug Administration, Room 1-23, 12420 Parklawn Drive, Rockville, MD 20857. This letter should not be considered a formal ruling on your petition. That occurs when you are sent a response by the Associate Commissioner for Regulatory Affairs.

We hope this information will be helpful.

Sincerely yours,

William E. Gilbertson, Pharm. D.
Director
Monograph Review Staff
Office of OTC Drug Evaluation
Center for Drug Evaluation and Research